REMARKS

Claims 3, 6-8, 10-30 and 33 are canceled as being drawn to a non-elected invention.

The specification has been amended to insert a Government Rights statement and to introduce the issued U.S. Patent number that corresponds to the PCT application number PCT/TJS95/01219 identified in the specification. Claims 40-41 have been amended to replace the designation "21-6" with the correct designation "21.6" as disclosed in PCT/TJS95/01219 and U.S. 5,840,299. No new matter has been added.

Claims 1, 2, 4, 5, 9, 31, 32 and 34-41 are pending and under examination.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 34-41 are rejected as indefinite in the recitation of antibodies designated "HP1/2", "HP2/1", HP2/4", "L25", "P4C2", "P4G9", "21-6" and "21.6" because, according to the Examiner, "its characteristics are not known." This rejection is respectfully traversed.

A skilled artisan, at the time of filing, would be aware that each of the recited antibody names identifies a particular, art known, anti-VLA-4 antibody. Applicants submit herewith Exhibit 1, which includes 23 abstracts from pre-priority date references, each of which refers to one or more of the recited anti-VLA-4 antibodies "HP1/2", "HP2/1", HP2/4", "L25", "P4C2" and "P4G9" by the same name as recited in the claims. (Of course, many more references can be found that refer to the anti-VLA-4 antibodies recited in the claims by but do so within the body of the reference and not in the abstract.) Of the references submitted herewith, many were published in the late 1980's and early 1990's, many years before the priority date of the present application. This shows that, at the time of priority, each recited antibody name was routinely used to identify one particular, widely used, art-known anti-VLA-4 antibody. Contrary to the Examiner's suggestion, the recited antibody names are not "merely a laboratory designation", as evidenced by the fact that the references in Exhibit 1 are from numerous different laboratories that identify the same source or origin when referring to a specific antibody. Therefore, at the time of filing and in the context of the specification, the skilled artisan would have correlated each antibody name recited in the claims with one particular, art-known anti-VLA-4 antibody.

With regard to the 21.6 antibody, the specification and claims have been amended to substitute the designation "21-6" with "21.6". The "21.6" designation refers to a particular antibody, the identity and sequence of which was known in the art and disclosed in PCT/TJS95/01219 and corresponding U.S. Patent No. 5,840,299. (Note the specification has been amended to introduce the issued U.S. Patent number in addition to the PCT application number). Thus, in the context of the specification, a skilled artisan would know precisely what antibody (indeed, what specific antibody sequence) the term 21.6 refers to.

Definiteness of claim language is analyzed, not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art. In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). See also MPEP 2173.02. In light of the foregoing, it is clear that a skilled artisan would have understood the identity of each of the recited antibodies from their recited name in the context of the specification. Accordingly, the skilled artisan would have understood the meaning and scope of the claims and a rejection for indefiniteness is not proper.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 34-41 are rejected as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner states that:

> An application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application. (. . .) Further, it is apparent that the antibodies 'HP1/2', 'HP2/1', 'HP2/4', 'L25', 'P4C2', 'P4G9', '21-6' and '21.6'. are essential and required to practice the claimed invention. As a required element, the hybridoma that secrete the [recited antibodies] must be known and readily available to the public or obtainable by a repeatable method set forth in the specification.

With regard to antibody "21-6", the rejection has been met by replacing references to "21-6" with the correct designation "21.6" and amending the specification to include the number of the issued U.S. patent corresponding to the PCT publication already provided in the specification, which describes the making and using of murine 21.6 anti-VLA-4 antibody in

detail, including the specific 21.6 sequences. With regard to other aspects of the rejection, the rejection is respectfully traversed.

Contrary to the Examiner's assertion, the antibodies 'HP1/2', 'HP2/1', 'HP2/4', 'L25', 'P4C2', and 'P4G9' were readily available to the public at the time of filing. Exhibit 1, discussed above, shows that 'HP1/2', 'HP2/1', 'HP2/4', 'L25', 'P4C2', and 'P4G9' were known in the art and available to the public (note that numerous different groups had published references using the recited antibodies). In addition, Applicants submit, as Exhibit 2, four technical data sheets showing that at least HP2/1, P4C2, P4G9 and L25 were available from at least one commercial source.

In view of the evidence provided herein and the teachings of the specification, it is clear that the 'HP1/2', 'HP2/1', 'HP2/4', 'L25', 'P4C2', 'P4G9', and '21.6' were readily available to the public at the time of filing. As such, a skilled artisan would be able to make and use the claimed methods without undue experimentation. Therefore, Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

I. Van Zaanen combined with other references

Claims 1, 2, 4, 5, 9, 31-32 and 34-39 are rejected as unpatentable over Van Zaanen in view of Masellis-Smith and Lokhorst and Owens. Claims 34-39 are rejected as unpatentable over Van Zaanen in view of Masellis-Smith and Lokhorst and Owens and further in view of U.S. Patent No. 5,932,214 and Kamata et al. This rejection is respectfully traversed.

The primary reference for all of the rejections under 35 U.S.C. §103 is Van Zaanen. Van Zaanen, as shown by the date stamped copy submitted herewith as Exhibit 3, has a publication date of August 18, 1998. Applicants reduced the claimed invention to practice prior to the effective publication date of this reference, as shown by the enclosed Declaration under 37 C.F.R.§ 1.131 of all the inventors (Exhibit 4). Therefore, Van Zaanen is not available as prior art against the present claims. Without Van Zaanen, a *prima facie* case of obviousness clearly cannot be made. Accordingly, Applicants respectfully request that this rejection be withdrawn.

II. Lee in view of U.S. Patent No. 5,932,214 and Kamata et al.

Claims 1, 2, 4, 5, 9, 31-32 and 34-39 are rejected as unpatentable over Lee (U.S. Patent No. 6,495,525) in view of U.S. Patent No. 5,932,214 and Kamata et al.

Lee discloses the use of a small molecule VLA-4 inhibitor (oMePUPA-V) to treat animal models of pulmonary inflammation (airway hypersensitivity) and delayed type hypersensitivity. Lee suggests that the small molecule inhibitor could also be used to treat "VLA-4-mediated cell adhesion and pathologies associated with that adhesion, such as inflammation and immune reactions" and lists 20 specific disorders within that class. U.S. 5,932,214 and Kamata et al. disclose various VLA-4 antibodies but do not relate to treatment of multiple myeloma. The Examiner argues that one of ordinary skill in the art would have been motivated to substitute the anti-VLA-4 antibodies disclosed by U.S. Patent No. 5,932,214 and Kamata for oMePUPA-V as disclosed in Lee to treat multiple myeloma because "Lee suggested the substitution implicitly because the compounds of the invention are inhibitors of VLA-4 integrin thereby blocking the binding of VLA-4 to its various ligand (*sic*), such as VCAM-1 and regions of fibronectin such [as] antibodies to VLA-4." This rejection is respectfully traversed. As discussed in more detail below and in the declaration under 37 C.F.R. § 132 of Dr. Blake Pepinsky, enclosed herewith as Exhibit 5 (hereinafter "the Pepinsky declaration"), oMePUPA-V is simply not interchangeable with anti-α4 integrin antibodies.

Lee states that oMePUPA-V can be used to treat:

> VLA-4-mediated cell adhesion and pathologies associated with that adhesion, such as inflammation and immune reactions, including for example, multiple sclerosis, asthma, allergic rhinitis, allergic conjunctivitis, inflammatory lung diseases, rheumatoid arthritis, septic arthritis, type 1 diabetes, organ transplantation, restenosis, autologous bone marrow transplantation, inflammatory sequelae of viral infections, myocarditis, inflammatory bowel disease including ulcerative colitis and Crohn's disease, certain types of toxic and immune-based nephritis, contact dermal hypersensitivity, psoriasis, tumor metastasis, *multiple myeloma*, and atherosclerosis. (Emphasis added.)

This list encompasses a very broad range of immune and inflammatory diseases in addition to multiple myeloma and tumor metastasis. While oMePUPA-V has an extraordinary

broad range of therapeutic applicability, there is simply no indication in Lee or in any other reference cited that an antibody inhibitor of α4 integrins, as recited in the claims (rather than a small molecule inhibitor), would have the same applicability. Contrary to the Examiner's argument, a skilled artisan would simply not be motivated to substitute an antibody disclosed in U.S. 5,932,214 or Kamata, for the small molecule drug of Lee. Specific reasons for this are summarized below and are discussed in detail in the Pepinsky declaration.

As discussed in the Pepinsky declaration, antibodies are completely different than small molecules. First, antibodies as a class of agent are vastly different in size than small molecule drugs such as oMePUPA-V. Due to its small size, a small molecule drug is typically directed to a "pocket" or specific docking site on the target molecule, where it may act as either an agonist or an antagonist. In contrast, antibodies are large molecules that, although they bind to a particular epitope, effectively cover a large surface area and thereby act to block a biological pathway though stearic hindrance, as opposed to binding a specific active site or pocket. As discussed in the Papinsky declaration, oMePUPA-V binds at the ligand binding site and therefore may act as an agonist. In contrast, none of the existing anti-α integrin antibodies bind directly at the ligand binding site. For this reason alone, a skilled practitioner would not have believed oMePUPA-V to be interchangeable with an anti-α4 integrin antibody.

Second, in contrast to oMePUPA-V, an antibody-based therapeutic would be expected to implicate aspects of the immune response in its effect. As discussed in detail in the Pepinsky declaration, the binding of Fc receptors by the Fc domain of an antibody molecule provides signals that activate and recruit immune and inflammatory cells, or, alternatively, that send inhibitory signals that downregulate immunity. The implication of additional immune mechanisms with an antibody could result in a completely different effect in vivo than that of oMePUPA-V. Thus, a skilled artisan would not have reasonably predicted that an anti-α4 integrin antibody would have the same effect as oMePUPA-V in vivo. Such antibody-specific mechanisms are an important reason why an antibody and a small molecule would not be considered interchangeable.

Third, anti-α4 integrin antibodies, as recited in the claims, have a different specificity than oMePUPA-V. Lee teaches that oMePUPA-V is highly specific for VLA-4 (having α4/β1

subunits) but does not act on α4/β7 integrin (Lee 7:39-42; 25:33-34). In contrast, the α4 integrin antibodies recited in the claims can bind both α4/β1 and α4/β7, implicating an additional integrin pathway. The broader specificity of an anti-α4 integrin, compared to oMePUPA-V, would have made it unpredictable that an anti-α4 antibody would have the same effect as oMePUPA-V in vivo at all, much less have the same applicability across such a broad range of disorders.

Moreover, Applicants note that Lee discloses experiments that use oMePUPA-V to treat animal models of pulmonary inflammation (airway hypersensitivity) and delayed type hypersensitivity (Lee, Examples 2-4). Lee lists a broad range of other immune and inflammatory diseases that can be treated with oMePUPA-V and also lists multiple myeloma and tumor metastasis. Multiple myeloma is a type of cancer (neoplasm) that develops in a subset of white blood cells but it is not an immune or inflammatory disorder *per se*, unlike the other disorders listed in Lee or the disorders treated in the *in vivo* examples in Lee. There is absolutely no motivation to select multiple myeloma from this long list in Lee to treat with an antibody. A skilled artisan would certainly not be motivated to use an antibody therapeutic to treat a neoplasm based on Lee's data showing that a small molecule drug against a target can be used to treat a disorder related to inflammation, or more particularly, to a hypersensitivity-type inflammatory response. Treating neoplasms with antibodies is a completely different area of medicine than treating immune- or inflammatory-mediated diseases with small molecule drugs. A skilled artisan would find absolutely no motivation in the combination of the cited references to use an anti-VLA-4 antibody to treat any cancer, much less a specific cancer such as multiple myeloma. Accordingly, Applicants request that the rejection be withdrawn.

Rejections Under 35 U.S.C. §101

Claims 1, 2, 4, 5 and 9 are provisionally rejected for statutory double patenting over claims 1, 2, 4, 5 and 11 of U.S.S.N. 09/943,659. Once the claims of the present application are deemed allowable, Applicants will address this rejection by canceling or amending the relevant claims of U.S.S.N. 09/943,659, or taking other appropriate action.

Obviousness-type double patenting

Claims 1, 2, 4, 5, 9 and 31-32 are provisionally rejected as unpatentable over claims 1, 2, 4-5, 9, 11-12, 17-18, 20-21, 25, 27, 34-35, 37 and 44 of co-pending U.S.S.N. 10/086,217. Claims 34-39 are provisionally rejected as unpatentable over claims1, 2, 4-5, 9, 11-12, 17-18, 20-21, 25, 27, 34-35, 37 and 44 of co-pending U.S.S.N. 10/086,217 in view of U.S. 5,932,214 and Kamata. Once the present claims are allowed, Applicants plan to remove and obviate the rejection by submitting a terminal disclaimer by the common Assignees of the present application and the '217 patent. A terminal disclaimer is not an admission or comment regarding the merits of the rejection. (Quad Environmental Technologies Corp. v. Union Sanitary District, 946 F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991)).

Enclosed is a Petition for Extension of Time along with the required fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 1/30/2004

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